In re Application of: Alexei SHIR et al
Serial No.: 10/535,189
Filed: September 21, 2006
Office Action Mailing Date: November 26, 2008

Examiner: Terra C. Gibbs
Group Art Unit: 1635
Attorney Docket: 29770

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 72-109 are pending in this case. Claims 72-95 have been withdrawn under a restriction requirement for a non-elected invention. Claims 96-98 have been rejected under 35 U.S.C. § 102 and Claims 96-109 have been rejected under 35 U.S.C. § 103. Claims 96, 103, 105 and 106 have now been amended. Claims 100, 101 and 102 have now been cancelled. New claims 110-114 have now been added.

In a telephone interview graciously granted by the Examiner, Applicant discussed proposed amendments to Claim 96 and explained why in light of the amendments the claims cannot read over ribozymes.

In said interview, the Examiner indicated that the proposed amendments do distinguish the claimed double stranded molecules from ribozymes.

35 U.S.C. § 102(a) Rejection

The Examiner has rejected Claims 96-98 as being anticipated by Abounader et al (FASEB Journal 2002, Jan; 16(1):108-10; Epub 2001 Nov 29).

The Examiner states that Abounader et al teach in vivo targeting of scatter factor/hepatocyte growth factor and/or c-met expression via U1snRNA/ribozymes in glioma cells. The Examiner further states that administration of the disclosed ribozymes brings about programmed cell death or apoptosis. The Examiner also notes that Aboundader et al teach that the ribozyme is associated with a nucleic acid carrier by ligation/annealing. The Examiner further states that the two complementary pairs of ribozyme sequences may be interpreted as being the targeting moiety, since the targeting moiety has not been defined.

The Examiner has also rejected Claims 96-98 as being anticipated by Czubzuko et al (Proc. Natl. Acad. Sci., 1996 Vol 93: 14753-14758).

The Examiner states that Czubzuko et al teach cell death by a ribozyme targeted to the secreted growth factor pleiotrophin. The Examiner further states that the two complementary pairs of ribozyme sequences may be interpreted as being the targeting moiety, since the targeting moiety has not been defined.

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The Examiner has further rejected Claims 96-98 as being anticipated by Zhao et al (Development, 1998 Vol. 125:1899-1907).

The Examiner states that Zhao et al disclose retinal cell death by a ribozyme construct targeted to neuregulin-1. The Examiner further states that the two complementary pairs of ribozyme sequences may be interpreted as being the targeting moiety, since the targeting moiety has not been defined.

The Examiners rejections are respectfully traversed.

As pointed out in the interview on the 26th of February 2009, the compositions for cell killing of the claimed invention rely on a particular type of double stranded RNA which mimics the activity of viruses in its ability to mediate apoptosis via up-regulating expression of interferon (IFN)-α/-β in cells. Ribozymes do not rely on this method for cell killing, but rather on its capability of cleave a nucleic acid in a sequence specific manner. As further pointed out in the interview, the double stranded RNA is also distinct from that of ribozymes since it consists of two strands of RNA. Ribozymes, on the other hand consist of a single strand of RNA which in certain places overlap to form a double stranded element.

The limitations of the presently claimed double stranded RNA are fully supported in the specification.

"2 strands" is supported on Page 18, lines 16-17

> *"The dsRNA molecule may be composed of a pair of RNA strands composed of a different number, or more preferably, the same number of ribonucleotides".*

"which induces viral-like double stranded RNA mediated apoptosis, triggered by up-regulation of interferon (IFN)-α/-β expression in said cell and/or tissue" is supported on Page 3, line 12-18.

> *" One of the mechanisms which virally infected cells employ to protect the body from infection involves triggering of apoptosis by dsRNA molecules which are generally and exclusively expressed in virally infected cells. Virally induced generation of dsRNA leads to up-regulation of interferon (IFN)-□/-□ expression. Interferon-□/□ are strong anti proliferative cytokines whose mechanism of action involves inducing expression of PKR*

and the 2'-5' OAS system for preventing the spread of the virus to cells adjacent to the infected cells."

Further, the claimed double stranded RNA is cytotoxic to **all** cells. As such, the cytotoxic element of the composition must be targeted to specific cell types using a targeting moiety to avoid non-specific cell killing. The targeting moiety of the claimed invention is a ligand or antibody. In contrast, the targeting moieties of ribozymes are single stranded RNA elements. Further, the targeting moiety of the claimed invention binds to a cell surface marker. Ribozymes on the other hand are not capable of binding cell surface markers, but rather to RNA encoding same.

The limitations of the presently claimed targeting moiety are fully supported in the specification.

"said targeting moiety being a ligand or antibody which binds to a cell surface marker being specific to the target cell and/or tissue" is supported on Page 22, line 5 and Page 21, lines 21-22.

Further, the targeting moiety has now been limited to one which is not covalently bound to the double stranded RNA. Support for such a claim amendment can be found on Page 20, lines 8-16.

As explained to the Examiner in the interview, the components of the compositions for cell killing and the interactions therebetween are such that they form particles which penetrate solid tumor tissue. This distinguishes the presently claimed composition of matter over compositions comprising ribozymes in a viral vector since the latter are not capable of penetrating solid tumor tissue.

The limitation of the presently claimed components being able to form particles capable of penetrating solid tumor are fully supported in the specification- see Page 14, lines 1-6.

> *"Furthermore, as is described hereinbelow and in the Examples section which follows, as a consequence of its optimal tissue penetration capacity, the composition-of-matter of the present invention can be used to kill with optimal efficiency and rapidity a target cell/tissue, such as a human glioblastoma cell/tissue, which is effectively impermeable to particles having the dimensions and/or surface chemistry of a viral vector ".*

"Particle" is supported on Page 14, lines 2-10.

> "*...as a consequence of its optimal tissue penetration capacity, the composition-of-matter of the present invention can be used to kill with optimal efficiency and rapidity a target cell/tissue, such as a human glioblastoma cell/tissue, which is effectively impermeable to particles having the dimensions and/or surface chemistry of a viral vector. Hence, the composition-of-matter of the present invention can be used to kill with optimal efficiency and rapidity a target cell/tissue which is not effectively amenable to killing via a cytotoxic particle such as a viral vector. As such, the method of the present invention overcomes various critical limitations of the prior art*".

To further differentiate the present invention from those using ribozymes, Claim 113 has now been added to limit the association of the targeting moiety to the nucleic acid carrier to a covalent association. Ribozymes (and the targeting moieties comprised therein), do not covalently bind nucleic acid carriers, but rather via electrostatic interactions.

Support for such an amendment may be found in the present specification.

> "*Preferably, the targeting moiety is covalently attached to the nucleic acid carrier*". page 20 lines 27-28.

Claims 110-112 have also been added to further differentiate the present invention from that of the art.

Support for Claim 110 can be found on Page 17, lines 1-2.

Support for Claim 111 can be found on Page 17, line 22.

Support for Claim 112 can be found on Page 54 lines 10-20.

Support for Claim 114 can be found in original claims 7, 14 and 17.

For the above reasons, Applicant contends that the above cited reference cannot be used to anticipate the presently claimed invention.

35 U.S.C. § 103(a) Rejection

Claims 96-109 have been rejected under 35 U.S.C. 103(a) as being obvious over WO 94/23050 in view of Yamazaki et al (Journal of the National Cancer

Institute, 1998, Vol. 90;581-587) and Ogris et al (Journal of Biological Chemistry, 2001, Vol 276: 47550-47555).

The Examiner states that WO94/23050 teaches a method of blocking RNA translation by administering a gene encoding an RNA which hybridizes and inhibits the function of a cellular RNA, the RNA being complexed with a carrier comprising a cell-specific binding agent and a gene-binding agent. The Examiner further states that WO94/23050 teaches the cell-specific binding agent is specific for a cell surface structure and the gene-binding agent is a compound such as a polycation. The Examiner further states WO94/23050 teaches that the antisense RNA is a ribozyme.

The Examiner states that the Yamazaki et al teach a method of killing cells by administering a ribozyme in a nucleic acid carrier. The Examiner states that the ribozyme comprises a targeting moiety by virtue of containing regions of complementary sequence.

The Examiner then goes on to suggest that it would be obvious to devise a method of cell killing based on the combined teachings of WO94/23050 and Yamazaki and further it would be obvious to include melittin based on the teachings of Ogris.

The Examiner's rejection is traversed.

Applicant respectfully urges that there is no motivation for combining the WO94/23050 reference with the Yamazaki reference and as such the Examiner has not put forward a *prima facie* case of obviousness.

WO94/23050 teaches administration of DNA and not RNA to block RNA translation.

Claim 1 of WO94/23050 reads as follows:

> *"A soluble molecular complex for targeting* ***a gene encoding*** *an antisense RNA to a specific cell, the complex comprising an expressible gene encoding an RNA which hybridizes to and inhibits the function of a cellular RNA,* ***the RNA being complexed with a carrier*** *comprising a cell-specific binding agent and a gene-binding agent".*

The claim specifies that the complex comprises a gene encoding an RNA and not the RNA itself. Since the molecular complex taught by WO94/23050 comprises

DNA and not RNA, Applicant contends that the second part of the Claim which specifies that the RNA is complexed with a carrier has not been drafted correctly. There is no RNA present to be complexed with the carrier. According to the MPEP Section 2106, the claim language should be interpreted in view of the specification. Accordingly, Applicant contends that the claim should read "gene encoding the RNA" and not "RNA".

Yamazaki et al, contrary to the presently claimed invention teaches a ribozyme that binds to an RNA encoding a cell surface, but not capable of binding the cell surface marker per se. Further, Yamazaki's targeting moiety is covalently bound to the double stranded ribozyme, whereas the presently claimed targeting moiety is not.

Applicant contends there is no motivation to combine the art of DNA with the art of RNA. Applicant further contends that the Examiner has not identified all the salient elements of the claims and the combination of WO94/23050 and Yamazaki cannot be used either alone or in combination with Ogris et al to obviate the presently claimed invention.

Accordingly, the *prima facie* case of obviousness is fully rebutted. Unless the Examiner can articulate objective reasons that the field is predictable, the rejection of the pending claims as obvious must be withdrawn.

In view of the above amendments and remarks it is respectfully submitted that claims 96-99 and 103-114 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: March 16, 2009

Enclosures:

- Petition for Extension (One Month)
- Request for Continued Examination (RCE)